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Pharmacokinetics of modified-release prednisone tablets in healthy subjects and patients with rheumatoid arthritis

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Key words: modified-release prednisone; pharmacokinetics; bioavailability; rheumatoid arthritis

Abstract

In rheumatoid arthritis (RA), nocturnal release of pro-inflammatory cytokines is not adequately counteracted by endogenous glucocorticoid, and is associated with symptoms of morning stiffness and pain. Taking exogenous glucocorticoid during the night reduces morning stiffness significantly more than treatment at the conventional time in the morning, though waking to take tablets is unacceptable for patients. Modified-release prednisone tablets ~~have been~~was developed to allow administration at bedtime for programmed delivery of glucocorticoid during the night. Single centre crossover studies were conducted, each in ≥ 24 healthy subjects, to compare the pharmacokinetics of a single 5 mg oral dose of modified-release prednisone and conventional prednisone, and the effect of food on bioavailability. There was no substantial difference in pharmacokinetic parameters of the formulations apart from the programmed delay in release of glucocorticoid from the modified-release tablets (C_{\max} 97%, $AUC_{0-\infty}$ 101%, 90% confidence intervals within the requisite range for bioequivalence). Administration after a full or light meal did not affect pharmacokinetic characteristics, but bioavailability was reduced under fasted conditions. Pharmacokinetic evaluation in nine patients with RA confirmed that modified-release prednisone tablets taken at bedtime (around 22:00 h) with or after an evening meal result in programmed release of glucocorticoid 4–6 hours after intake.

The circadian pattern in symptoms is a well-known feature of rheumatoid arthritis (RA).^{1, 2} Typically, patients experience joint stiffness and pain in the morning; it lasts for more than an hour in 24–49% of patients.^{1, 2} Stiffness may be present even in patients in remission or with minimal disease activity.¹ Morning symptoms may impair functional abilities, with adverse impact on wellbeing.³ Furthermore, working ability may be impaired, with severity of morning stiffness a key factor in early retirement from work in the 3 years after RA diagnosis.^{3, 4} Yet despite the widespread occurrence of morning stiffness and its impact on patients, treatment is often unsatisfactory.⁵

There is increasing awareness of the underlying pathophysiology of morning symptoms in RA.^{6, 7} Nocturnal levels of the pro-inflammatory cytokine, interleukin-6 (IL-6) correlate with morning stiffness.^{8, 9} In patients with RA, the normal nocturnal increase in endogenous cortisol appears to be insufficient to counteract increased nocturnal levels of IL-6.^{6, 7, 10} Exogenous glucocorticoid may be given to supplement endogenous glucocorticoid.^{7, 11} Prednisone and its therapeutically-equivalent metabolite, prednisolone, are oral glucocorticoids commonly used in RA.^{11, 12} Both glucocorticoids have a short half-life of approximately 2 hours and are usually administered in the morning.¹³ However, efficacy with respect to morning stiffness and pain is improved if treatment is given during the night,¹⁴ before the peak in IL-6, though it is unacceptable in the long term for patients to have to wake to take medication.

To facilitate delivery at the optimal time, in accordance with circadian rhythms, a modified-release formulation of prednisone has been developed.¹⁵ These tablets, consisting of an active drug core inside an inert coat, are designed for administration at bed time (approximately 22:00 h). After a lag period during which it absorbs fluid, the coat opens to allow drug release at approximately 02:00 h. Clinical studies have demonstrated a reduction in the duration of morning stiffness following administration of modified-release prednisone compared with placebo and the same dose of

conventional prednisone administered in the morning.^{8, 9, 15-17} Studies were undertaken in healthy subjects to compare the pharmacokinetic characteristics of modified-release prednisone with conventional prednisone and to assess the impact of food on bioavailability. Another study, conducted to investigate the influence of modified-release prednisone on circadian IL-6 plasma levels using 24-h blood sampling in nine patients with RA, also included analysis of plasma prednisone levels. Results reporting the clinical findings and IL-6 levels have been reported previously.^{8, 9} The findings on prednisone plasma levels are reported here to provide additional insight into the pharmacokinetic characteristics of modified-release prednisone. ~~was conducted to confirm the pharmacokinetic characteristics in patients with RA taking modified-release prednisone under practical conditions.~~

MATERIALS AND METHODS

Studies conducted in healthy subjects were each carried out at a single centre (the key study, KS1, and supportive study, SS1: Antwerp, Belgium; supportive studies SS2 and SS4: Berlin, Germany; supportive study SS3: Miami, USA). The study in patients (P1) was also conducted at a single centre (Bristol, UK). Written informed consent was obtained from all subjects. All study designs received ethical approval. Studies were conducted in accordance with the Declaration of Helsinki and with local applicable laws and guidelines.

Subjects

All healthy subjects were non-smokers aged over 18 years and were of general good health as evidenced by medical and drug history, body mass index, physical examination, 12-lead electrocardiograms, vital signs and safety laboratory variables. No concomitant drug intake was allowed. In the study of nine patients with RA, stable medication for the management of the disease was permitted.

Formulation

Modified-release prednisone tablets (**Lodotra®**), as formulated for commercial use (i.e. *in vitro* lag period of 3.5–4.5 h, mean 3.9 h), were used in all studies at a dose of 5 mg. In addition, developmental formulations with *in vitro* lag period of 3.0–3.5 h, 4.0–5.0 h and 4.5–5.5 h (mean *in vitro* lag time of 3.2 h, 4.4 h and 4.9 h, respectively) were evaluated in supportive study SS4.

Conventional prednisone tablets 5 mg (Decortin®, Merck KGaA, Darmstadt, Germany) were used in the key study, KS1, and supportive studies SS1 and SS2.

Study designs

All studies in healthy subjects were single-dose, open-label, ~~randomised~~, crossover design. In all studies, the allocation of subjects to treatment sequence was randomised. The washout period between treatment arms was at least 3 days, with follow-up 3–9 days after the last treatment.

Treatments were swallowed whole with 240 mL of room temperature tap water with subjects in a standing position at administration and for the following 10 mins.

The key study (KS1) was a three-arm crossover study designed to reflect the relevant clinical comparison, namely conventional prednisone taken in the fasting state with evening administration of modified-release prednisone taken after either a light or a full meal. The sequence for allocation to each of the three treatment periods was according to a randomisation list (SAS Plan procedure). The primary objective of this study was to compare the bioavailability of prednisone and prednisolone from the reference formulation (conventional prednisone) and the test formulation (modified-release prednisone) after a light or full meal. The secondary objective was to assess the effect of food on the pharmacokinetic profile and bioavailability of modified-release prednisone.

~~allowed direct comparison of tablets formulated for commercial use after a full meal and a light meal, and direct comparison with conventional prednisone taken in the fasting state.~~

The timing of the dose and prior food intake varied in the supportive studies (SS1 – SS4), as summarised in **Table 1**, allowing direct comparisons to be made within the studies, and indirect comparisons between studies.

In the study conducted in patients with RA (P1), modified-release prednisone tablets 5 mg were taken once daily for 14 days. Patients were asked to take the treatment in accordance with the summary of product characteristics i.e. at bedtime (approximately 22:00 h), with or after an evening meal; if 2–3 hours had passed since the meal, the treatment was to be taken with a light snack. Patients were instructed not to take modified-release prednisone tablets in the fasting state.

Sample collection and analysis

In all studies, blood samples were collected before and at intervals throughout the 24-h following drug administration to measure plasma levels of prednisone and the active metabolite, prednisolone. In-dwelling cannulas were used to facilitate collection and minimise trauma. Samples (5 mL) of blood from healthy subjects (studies KS1 and SS1 – SS4) were collected into tubes containing lithium heparin, centrifuged (4°C, 2500 rpm, 15 mins). Samples of blood from patients with RA (study P1) were collected into chilled ethylenediaminetetraacetic acid and centrifuged (room temperature, 5750 rpm, 7 mins). In all studies, plasma was transferred to two polypropylene tubes for storage at –20°C. Frozen samples were analysed using a liquid chromatography/tandem mass spectroscopy method with limit of quantification (LOQ) of 0.25 ng/mL for prednisone and 1 ng/mL for prednisolone.

Pharmacokinetic analysis

Absorption profiles were determined from the prednisone serum concentrations using Thermo Scientific Kinetica software (version 4.4.1), using the Wagner-Nelson modified template. Pharmacokinetic parameters were derived from plasma concentrations of prednisone and prednisolone, calculated according to standard methods using WinNonlin Professional Edition (version 3.0) with all deviations from theoretical sampling times taken into account in the analysis. Pharmacokinetic parameters (except t_{\max} : time to maximum plasma concentration and t_{lag} : last time point with concentration below LOQ) were log-transformed and analysed by analysis of variance (ANOVA) with subject, sequence, period and treatment as factors. The mean square error of the ANOVA derived from C_{\max} (maximum observed plasma concentration) and $AUC_{0-\infty}$ (area under the plasma concentration versus time curve from time 0 extrapolated to infinity) were used to calculate the 90% confidence intervals for the difference between treatments in each study, on the log scale. Estimates of ratios between treatments were obtained by back-transformation. The time parameters, t_{\max} and t_{lag} were analysed using non-parametric methods.

RESULTS

Subjects

A total of 135 healthy subjects (116 men, 86%) and nine patients with RA (three men, 33%) participated in the studies. ~~Demographic information for the healthy subjects included in s~~Studies KS1 and SS1 – SS4 each included 24 or more subjects (range 24–28) of normal body mass; studies KS1, SS1 and SS4 were restricted to male subjects only. The mean age of subjects in each study ranged from 32 years (SS1) to 51 years (SS3); the overall age range of individuals included in the studies was from 18 years to 60 years. is summarised in Table 2. In the study conducted with patients (P1), the mean age of the nine subjects (three male and six females) was 65 years (range 51–79 years). Mean duration of RA ~~in the patient study (P1)~~ was 17.2 years; two patients had

recently diagnosed disease (duration ≤ 2 years) ~~with and~~ all others ~~having had~~ disease duration ≥ 16 years. Five patients were seropositive and all patients had evidence of erosions. Two patients smoked, three were ex-smokers and four patients were non-smokers. Seven patients were on concomitant therapy with disease-modifying antirheumatic drugs (DMARDs) and seven with non-steroidal anti-inflammatory drugs (NSAIDs).

Pharmacokinetic comparison between modified-release prednisone and conventional prednisone

In the key study allowing direct comparison (KS1), there was no visible difference in the prednisone absorption profile (**Figure 1**) and plasma concentration profile with conventional and modified-release tablets (**Figure 2**), apart from the programmed delay in release of glucocorticoid. Compared with conventional prednisone, modified-release prednisone taken after a light meal had a lag time of 3.5 h (90%CI: 3.3–3.8 h) with peak plasma concentration ~~after at 46.0 h (90% CI: 3.5–4.5 h)~~ (**Table 32**). As with conventional prednisone, $>80\%$ of drug was released from modified-release prednisone tablets within 2 h of opening. The rate and extent of absorption were bioequivalent, with C_{\max} of 97% and $AUC_{0-\infty}$ of 101% for prednisone from modified-release tablets relative to conventional tablets, and 90% confidence intervals for both key parameters within the requisite range (80–125%). Similar findings were observed for plasma levels of the active metabolite, prednisolone (**Table 32**).

The key study, KS1, compared evening administration of modified-release prednisone (20:00 h) directly with night time administration of conventional prednisone (02:00 h). However, conventional prednisone is usually taken in the morning. A supportive study (SS1) allowed direct comparison of morning (08:00 h) and night time (02:00 h) administration of conventional prednisone. In this study, C_{\max} and $AUC_{0-\infty}$ values were about 20% lower with morning dosing than night time dosing (geometric mean C_{\max} ~~16.817~~ vs ~~20.621~~ ng/mL; $AUC_{0-\infty}$ ~~93.994~~ vs 108 h.ng/mL). Another supportive study (SS2) allowed direct comparison of modified-release prednisone taken as

licensed (at 22:00 h after a light meal) and conventional prednisone taken as usual (08:00 h after breakfast) and confirmed that the pharmacokinetic characteristics of the two preparations are essentially the same ($AUC_{0-\infty}$: 90%, C_{max} : 99%) apart from a lag time of approx 4 h. The difference between treatments was 4.5 h for t_{lag} and 3.5 h for t_{max} .

Impact of food on pharmacokinetics of modified-release prednisone

In a direct comparison, the absorption of prednisone from the modified-release tablets was the same in healthy subjects taking the medication immediately after a full evening meal and a few hours after a light meal (key study KS1, data not shown). Indirect comparison with supportive study SS3 suggested that a high-fat meal did not appear to enhance absorption further (data not shown).

The impact of food on plasma levels of prednisone are shown in **Figure 3a** (direct comparison of dosing in the evening after a main meal and a few hours after a light meal, using data from the key study, KS1) and **Figure 3b** (direct comparison of the fed and fasted state from supportive study SS3).

There was no statistically significant effect of dosing after a main meal or a few hours after a light meal, with C_{max} in the fed state 108% (90% CI: 96–122%) relative to the light meal and relative bioavailability of 112% (90% CI: 100–125%) for $AUC_{0-\infty}$. However, there was a 3- to 4-fold reduction in bioavailability under overnight fasted conditions compared with the fed state after a full breakfast.

Consistency between studies and subjects

Despite the variations in dosing time and dietary state prior to administration of the modified-release tablets, indirect comparisons between studies suggested that there was broad consistency in the key pharmacokinetic parameters. The absorption profile of modified-release prednisone was determined in studies KS1, SS2, SS3 and SS4. In all studies, the profiles were consistent with the

expected results from the *in vitro* lag period (3.5–4.5 h). In supportive study SS4, which included developmental formulations as well as the commercial formulation of modified-release prednisone, *in vivo* lag times were approximately 1 h longer than the *in vitro* lag times and closely correlated (correlation coefficients of 0.96–0.98). The plasma concentrations of prednisone and derived pharmacokinetic parameters were comparable in the four studies of healthy subjects taking modified-release prednisone after a full meal (**Table 42**).

Three of the 27 subjects (11%) included in the pharmacokinetic analysis of supportive study SS2 showed plasma concentration of prednisone/prednisolone after administration of modified-release prednisone that were significantly below average. Variability in data arising from these three subjects resulted in 90% CI for the difference in geometric means of C_{\max} and $AUC_{0-\infty}$ for the treatments being outside the range of 80–125% (modified-release prednisone relative to conventional prednisone, C_{\max} : ~~98.799%~~, 90% CI ~~78.879–123.7124%~~; $AUC_{0-\infty}$: ~~89.990%~~, 90% CI ~~69.870–1165.8%~~). However, reanalysis omitting these outliers-extreme values resulted in 90% CI within the required range for equivalence. Low absorption was also observed in eight of the 108 doses taken (7%) in study SS4, which investigated tablets with different *in vitro* lag times. These outliers-extreme values were distributed at random between subjects and treatment groups. The variability in data meant that test formulations were not bioequivalent to the commercial formulation, using formal bioequivalence criteria. However, there was consistency in C_{\max} and $AUC_{0-\infty}$ when such outliers-extreme values were excluded, indicating that the *in vitro* lag time in the selected range (3.0 – 5.0 h) did not affect bioavailability.

Pharmacokinetics of modified-release prednisone in patients with RA

Pharmacokinetic parameters in patients with RA (study P1) confirmed the findings with healthy subjects. Six of the nine patients showed a steep rise in prednisone concentration after 4.75 h,

indicating that the modified-release prednisone tablet had opened by this time; the remaining three patients showed a rise in the blood sample an hour later, as shown in **Figure 4**.

DISCUSSION

The studies reported here, conducted in both healthy subjects and patients with RA, demonstrated that modified-release prednisone tablets give programmed delivery of glucocorticoid 4–6 hours after intake. All other pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max} , absorption curves) are close to values for the same dose of a conventional immediate-release tablet formulation, thus meeting the formal definition of bioequivalence if the conventional preparation is taken 4–6 hours after the modified-release formulation. These special pharmacokinetic characteristics allow modified-release prednisone tablets to be taken at bed time (approximately 22:00 h) to deliver anti-inflammatory glucocorticoid in the early morning hours (approximately 02:00 h) at the optimal time to counteract the nocturnal rise in pro-inflammatory cytokines.

There are some limitations in the studies reported here. Each study was small in size and the different conditions and administration times make a direct comparison between studies difficult. Nevertheless, the studies consistently showed similarity with conventional prednisone (except for the programmed lag period) and little difference between administration after small or large meals.

The study in patients (P1) enrolled only nine subjects for a study with the primary objective of assessing circadian IL-6 levels as ~~the protocol requiring determination of pharmacokinetic parameters requires~~ repeated measurements throughout a 24-h period so is onerous on patients and medical staff. Nevertheless, the pharmacokinetic profile of prednisone obtained ~~findings~~ from this small clinical study ~~were~~ was consistent with results in healthy subjects. Furthermore, modified-release prednisone in these nine patients was shown to suppress the early morning rise in IL-6, enhance the nocturnal levels of endogenous cortisol and significantly reduce morning stiffness, pain

and inflammatory markers ($p \leq 0.028$).^{8,9} The reported efficacy in clinical studies¹⁵⁻¹⁷ also confirms that the programmed delivery of glucocorticoid from modified-release prednisone tablets occurs in a satisfactory manner in patients with RA.

In two supportive studies in healthy subjects, the occurrence of a small number of outliers-extreme values was observed. In study SS4, modified-release prednisone was evaluated in all treatment arms, with 7% of doses resulting in low absorption. In the modified-release prednisone treatment arm of study SS2, three subjects (11%) showed low absorption. Such reduced absorption may be due to variability in gastric emptying and rapid transit of the tablet through the gastrointestinal tract with release of the active drug from the tablet in an area of low absorption (e.g. the colon). The findings from the clinical study suggests a greater variation in absorption rate for patients than healthy subjects, though these patients were older and varied considerably more than healthy subjects in age, smoking status and other characteristics. Patients were advised to take the medication at approx 22:00 h, but as in clinical practice, there were no checks on adherence with instruction. Despite the variability, the lag period for release of prednisone was still within the target range of 4–6 h. It seems likely that any variability in pharmacokinetic characteristics would have little clinical relevance. The intra-individual comparison in study SS4 indicated that low absorption profiles were distributed at random throughout treatment groups and subjects. It thus appears unlikely that this variability has any relevance to the practical use of this modified-release formulation. In the phase III clinical trial, the proportion of patients with no morning stiffness after 9–12 months of treatment with modified-release prednisone increased from 0 to 17% and those with stiffness for less than an hour increased from 10% to 29%.¹⁷ Conversely, the proportion of patients with prolonged morning stiffness fell; at the end of the study, 10% of patients reported morning stiffness lasting more than 3 hours (down from 33%) and 26% reported stiffness of 1–3 hours (down from 46%). These findings suggest that the majority of patients responded to

treatment. Furthermore, guidelines stress the importance of monitoring the patient's response to treatment.¹⁸ Consequently, any variability within a patient that consistently results in unsatisfactory clinical response should be identified and treatment should be adjusted accordingly.

The studies evaluated the impact of food on the pharmacokinetic parameters of modified-release prednisone. Bioavailability was reduced in fasted subjects compared with those who had eaten a few hours before drug administration, but there was no substantial difference between a full or light meal. Consequently, as advised in the summary of product characteristics, modified-release prednisone tablets should be taken after a light snack if it is more than 2–3 hours since last meal, and should not be taken in the fasted state.

Modified-release prednisone differs markedly in mechanism of release from enteric-coated prednisolone. The release of drug from enteric-coated tablets is dependent on pH and location within the gastrointestinal tract, whereas the release of prednisone from modified-release tablets relies on the absorption of fluid into the inert coat, which is time-dependent but not pH-dependent. Food has been shown to interfere with both the absorption and the pharmacokinetics of prednisolone from enteric-coated tablets, resulting in considerable variability in plasma levels.¹⁹ In a study of healthy volunteers taking enteric-coated prednisolone after a meal, in some subjects absorption of prednisolone was delayed for 12 h and remained at a measurable level for 24 h, while in others a normal pattern (as observed after fasting) was observed. Furthermore, unlike modified-release prednisone tablets, enteric-coated tablets do not address the need for programmed delivery of glucocorticoid to match the circadian rhythm of endogenous cortisol release.

There is growing realisation that circadian rhythms play a role in a number of conditions, prompting the use of timed therapeutic interventions (chronotherapy). In essential hypertension, taking an

angiotensin-converting enzyme (ACE) inhibitor at bedtime significantly increased the proportion of patients with controlled ambulatory blood pressure compared with the same dose taken in the conventional manner, in the morning.²⁰ Furthermore, bed time dosing significantly reduced blood pressure during the night, which has been shown to be a more relevant marker of cardiovascular risk than mean diurnal blood pressure. In hypercholesterolaemia, statins taken at night appear to be more effective than the same treatment taken during the day.²¹ Such approaches have the potential to increase efficacy of existing therapies, by optimising the administration regimen. In RA, this may allow prolongation of treatment with relatively inexpensive therapies before much more costly interventions (e.g. biological therapies) are required.²²

In conclusion, the studies reported here demonstrate that the pharmacokinetics of modified-release prednisone are essentially unchanged from conventional prednisone, apart from a programmed 4–6 hour delay in glucocorticoid release. This important feature allows medication to be taken at bed time resulting in improved clinical effects during the night, when required. Drug absorption and pharmacokinetics are similar irrespective of administration after a full or light meal. Findings in healthy subjects have been confirmed in patients with RA.

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Table 1. Summary of ~~treatment times and prior food intake in the key study (KS1), supportive studies in healthy subjects (SS1—SS4) and a study of patients with RA (P1)~~studies

Studies	N	Treatment arms			
		Prednisone 5 mg	Time of administration	Fed state	Prior food intake
Key study in healthy subjects					
KS1	27	Modified-release	20:00 h	Semi-fed	Light meal at 17:30
		Modified-release	20:00 h	Fed	Dinner at 19:30 h
		Conventional	02:00 h	Fasted	No food for >10 h
Supportive studies in healthy subjects					
SS1	28	Conventional	08:00 h	Fasted	No food for >10 h
		Conventional	02:00 h	Fasted	No food for >10 h
SS2	28	Modified-release	22:00 h	Fed	Dinner at 21:00 h
		Conventional	08:00 h	Fed	Breakfast at 07:30 h
SS3	24	Modified-release	08:00 h	Fasted	No food for >10 h
		Modified-release	08:00 h	Fed	High-fat breakfast at 07:30 h
SS4	28	Modified-release	22:00 h	Fed	Dinner at 21:00 h

		Modified-release*	22:00 h	Fed	Dinner at 21:00 h
<hr/>					
Study in patients with RA					
P1	9	Modified-release	22:00 h (approx.)	Fed/semi-fed	Dinner/light meal within 2–3 h
<hr/>					

*Three formulations assessed with different *in vitro* lag times (3.0–3.5 h, 4.0–5.0 h and 4.5–5.5 h)

Table 2. Demographic characteristics of subjects and patients included in the studies

	Studies in healthy subjects					Patients with RA
	KS1	SS1	SS2	SS3	SS4	P1
No. of subjects, n	27	28	28	24	28	9
No. of males, n (%)	27 (100%)	28 (100%)	21 (75%)	12 (50%)	28 (100%)	3 (33%)
Age						
–Mean, years (\pm SD)	34.8 (9.7)	31.5 (9.1)	34.0 (7.5)	51.4 (7.1)	34.7 (7.0)	64.6 (9.5)
–Range, years	20–48	18–46	20–45	32–60	21–45	51–79
Body weight						
–Mean, kg (\pm SD)	75.0 (9.5)	75.0 (9.8)	75.2 (11.1)	73.2 (8.8)	78.8 (8.8)	74.6 (16.9)
–Range, kg	58.2–92.3	58.9–98.3	56.3–97.4	57.8–98.0	64.1–98.5	48.4–103.4

Table 32. Pharmacokinetic parameters for prednisone and prednisolone in blood after a single oral dose of conventional prednisone 5 mg or modified-release prednisone 5 mg following a light meal (key study KS1) and for prednisone after modified-release prednisone 5 mg following a full meal (studies KS1 and SS2–4)

Pharmacokinetic	Prednisone					Prednisolone					<u>Prednisone after full meal</u>			
parameters	Conventional	Modified-release	Comparison	modified-release vs		Conventional	Modified-release	Comparison	modified-release vs		<u>KS1</u>	<u>SS2</u>	<u>SS3</u>	<u>SS4</u>
		(after light meal)		conventional			(after light meal)		conventional					
			Point	90% CI*	P**			Point	90% CI*	P**				
			estimate					estimate						
C _{max} , ng/mL	20.7 21 (19.0–	20.2 (18.5–19.9)	97%	86–110%	0.54	135 (124–147)	113 (104–123)	84%	74–94%	0.036	<u>22</u>	<u>18</u>	<u>19</u>	<u>17</u>
t _{max} , h	22.5 23)	21.9 22)	4.0 h	3.5–4.5 h	<0.0001	1.0 (0.5–3.0)	5.0 (4.0–9.0)	4.3 h	4.0–4.8 h	<0.0001	<u>6.5</u>	<u>7.0</u>	<u>7.0</u>	<u>8.0</u>
t _{lag} , h	2.0 (1.0–4.0)	6.0 (4.5–10.0)	3.5 h	3.3–3.8 h	<0.0001	0.0 (0.0–0.5)	3.5 (2.0–5.5)	3.5 h	3.3–3.8 h	<0.0001	<u>4.0</u>	<u>4.5</u>	<u>4.5</u>	<u>5.0</u>
AUC _{0–∞} , h.ng/mL	0.0 (0.0–0.5)	3.5 (2.0–5.5)	101%	90–113%	0.15	626 (583–672)	574 (535–617)	92%	83–101%	0.076	<u>126</u>	<u>109</u>	<u>103</u>	<u>103</u>
	109 (101–118)	110 (101–119)												

Values given are least-squares geometric means (90% CI) except for t_{max} and t_{lag}, which are given as median (range)

*90% CI for the ratio of the true averages derived for pharmacokinetic parameters (derived from ANOVA for continuous parameters and derived from Wilcoxon signed rank test for t_{max} and t_{lag})

**P value probability associated with the hypothesis of no significant difference between formulations (ANOVA except for t_{max} and t_{lag}: Friedman test)

Table 4. Summary of pharmacokinetic parameters for prednisone following administration of a single dose of modified release prednisone 5 mg after a full meal in healthy subjects

Pharmacokinetic parameters	KS1	SS2	SS3	SS4
C_{max} , ng/mL	22.2 (3.7)	17.8 (6.1)	19.1 (3.2)	16.6 (7.2)
t_{max} , h	6.50 (1.11)	7.00 (0.94)	6.90 (1.14)	7.90 (1.89)
t_{lag} , h	3.87 (0.39)	4.61 (0.66)	4.46 (0.62)	5.08 (1.26)
$AUC_{0-\infty}$, h.ng/mL	126.0 (24.3)	109 (39.4)	103.0 (18.9)	103.2 (43.5)
$t_{1/2}$, h	2.43 (0.29)	2.55 (0.47)	2.54 (0.45)	2.72 (0.47)
Values given are means (SD)				

Figure 1. Absorption of prednisone after a single oral dose of conventional prednisone 5 mg and modified-release prednisone 5 mg (key study KS1)

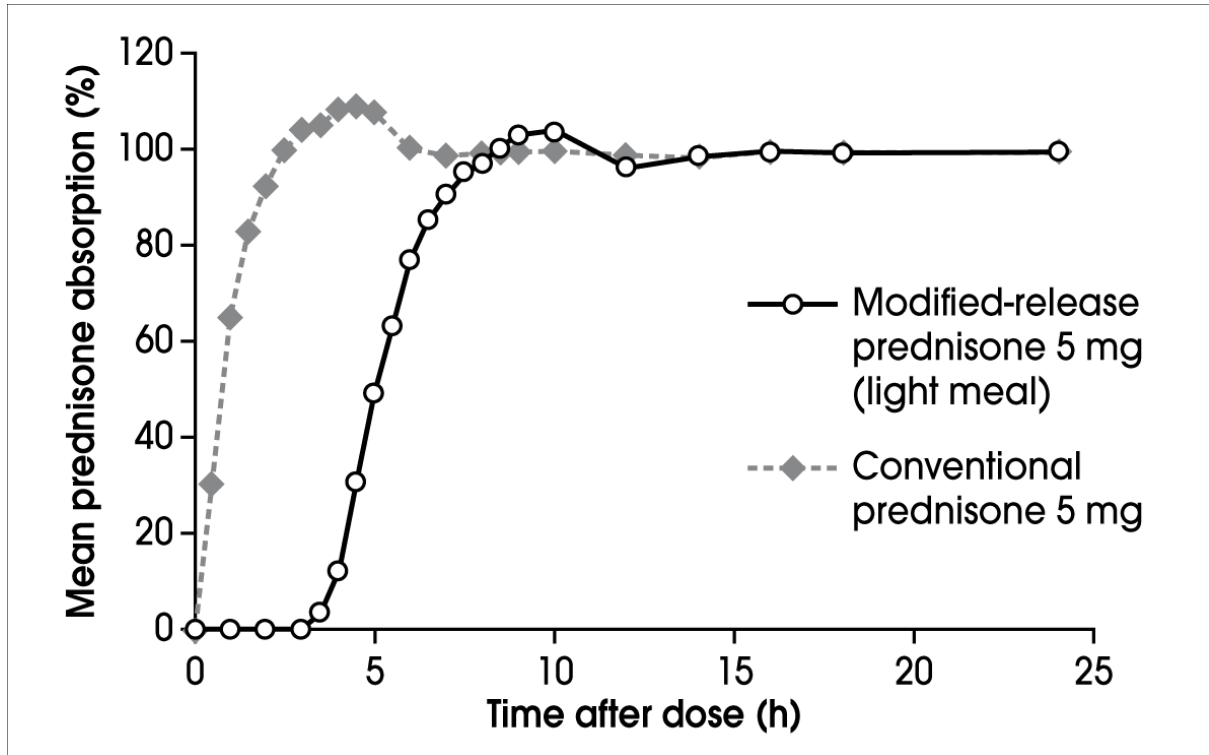


Figure 2. Mean concentration of prednisone in plasma after a single oral dose of conventional prednisone 5 mg and modified-release prednisone 5 mg (key study KS1)

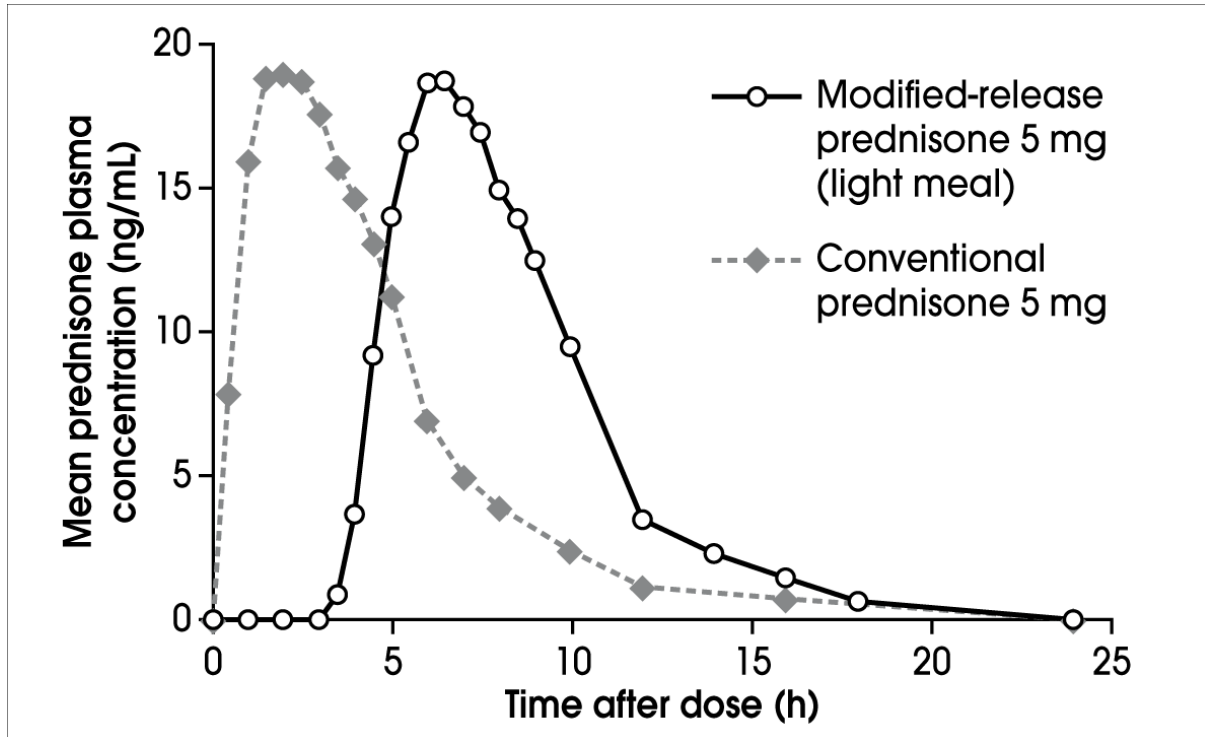
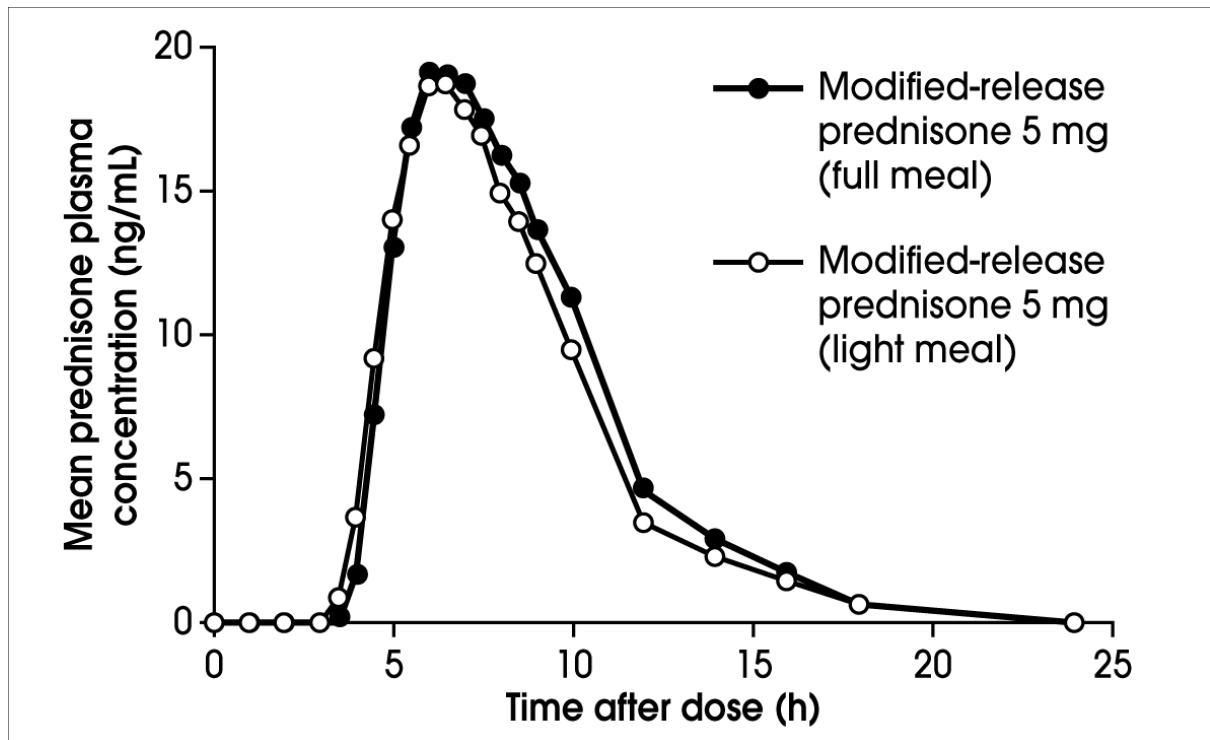
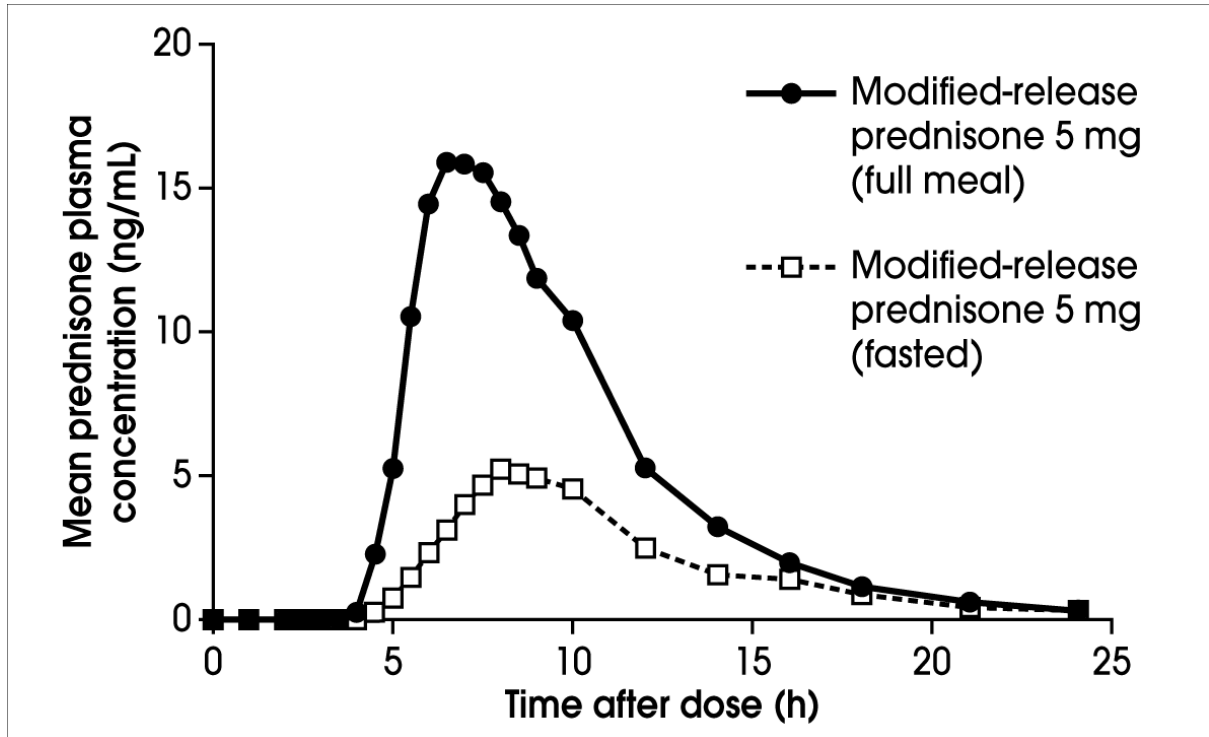


Figure 3. Impact of food on mean concentration of prednisone in plasma after a single oral dose of modified-release prednisone 5 mg

a) Full meal vs light meal (key study KS1)



b) Full meal vs fasted (supportive study SS3)



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